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GB 1456349 A GB 1441747 A EP 0271306 A2
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(54) Veterinary composition for treating mastitis

(57) Composition for treating mastitis in dry cows comprises an antibacterial and a seal composing a gel base containing a heavy metal salt. Administration is by the intramammary route. Antibacterial may be a penicillin. Salt is e.g. bismuth subnitrate and gel may be based on aluminium stearate. Seal and antibacterial can be kept separate.

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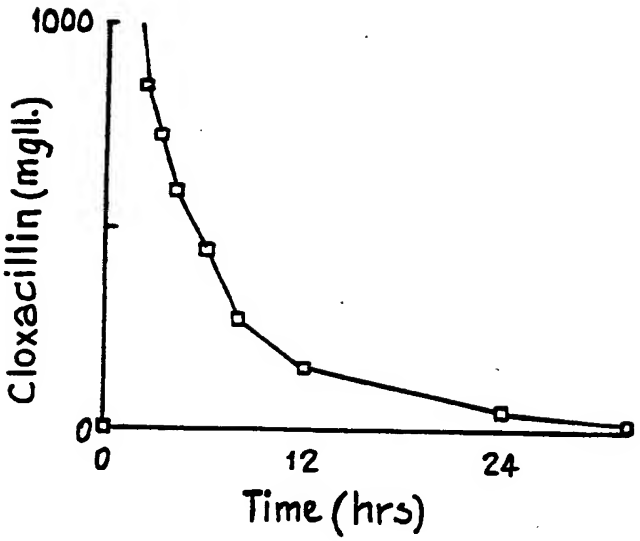
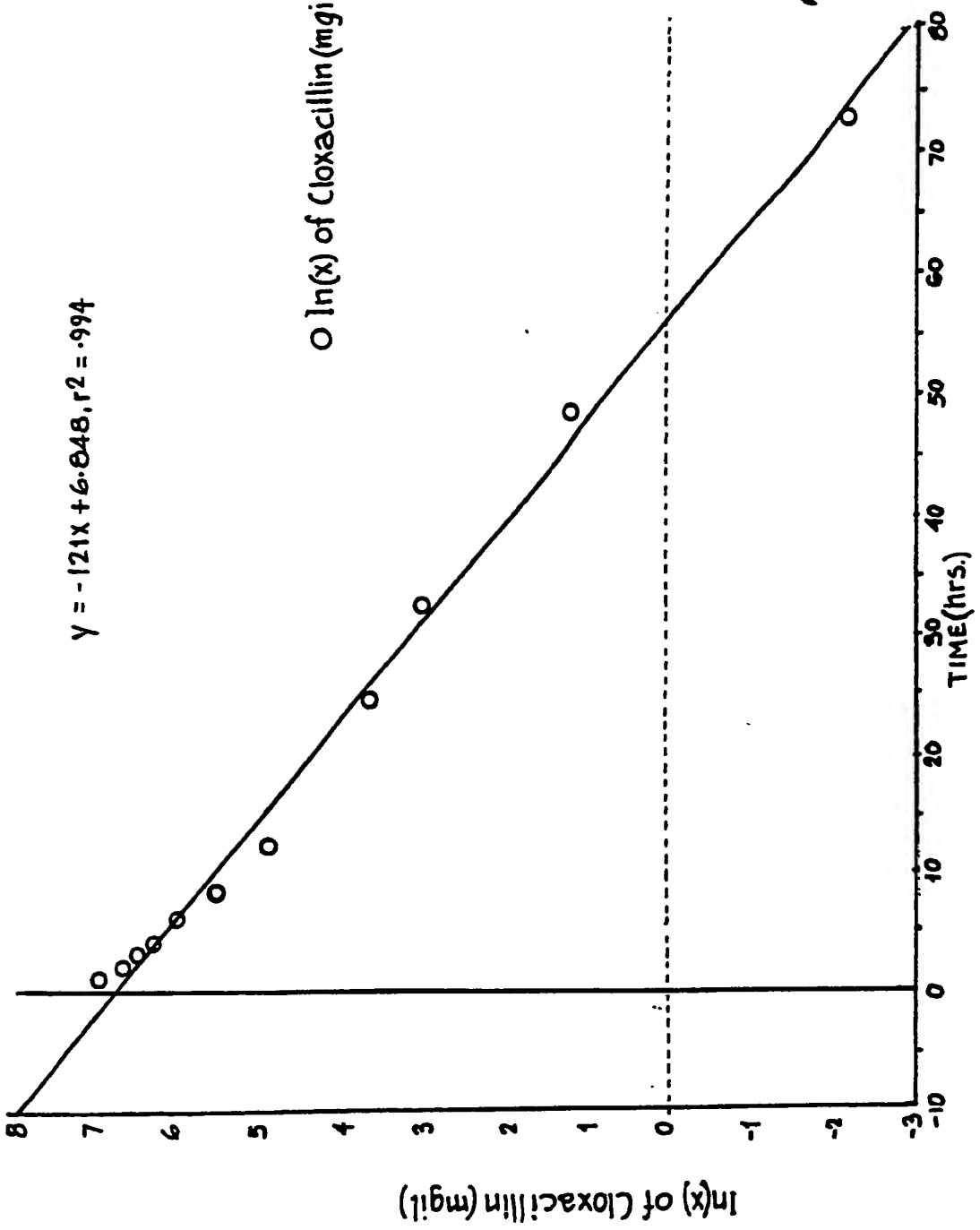


Fig. 1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O ln(x) of Cloxacillin (mgil)
ln(x) of Cloxacillin (mgil)
TIME(hrs.)
8
7
6
5
4
3
2
1
0
-1
-2
-3
-10
0
10
20
30
40
50
60
70

Fig. 2

"A Veterinary Composition"

The invention relates to a veterinary composition, particularly for the prophylaxis and treatment of mastitis in cows.

Bacterial infection via the teats of a cow is the most common cause of mastitis.

It is known to treat teats of a cow with a long acting antibiotic with effective cover only being provided whilst minimum inhibitory concentration (MIC) levels of the antibiotic are maintained. This period of cover can vary from 4 to 10 weeks.

It is also known to provide a physical barrier in the teat canal to try to prevent the ingress of pathogens. One such system is described in UK 1,441,747 (Lazonby).

One commercially available barrier system comprises a twin injector pack, one injector containing an antibiotic formulation and a second injector containing a barrier or seal formulation. The antibiotic formulation comprises penicillin salts and dihydrostreptomycin which is infused into the udder following the last lactation and before the cow is dried off. The seal formulation comprises a gel of aluminium stearate and liquid paraffin containing approximately 35% by weight of bismuth subnitrate. This is infused into the udder after the antibiotic formulation to seal the teat canal.

This invention is therefore directed towards providing an improved veterinary composition for the prophylaxis and treatment of mastitis in dry cows.

According to one aspect of the invention provides a veterinary composition for intramammary use in non-human animals comprising an antibacterial formulation, and a seal formulation, the seal formulation comprising a gel base and a non-toxic heavy metal salt in the base, wherein the heavy metal salt is present in an amount of at least 40% by weight of the base.

Preferably, the heavy metal salt is present in an amount of between 50% and 75% by weight, must preferably approximately 65% by weight.

In a preferred embodiment of the invention the heavy metal salt is bismuth sub-nitrate.

In one embodiment of the invention the base is a gel based on aluminium stearate. Preferably in this case the gel includes a vehicle such as liquid paraffin.

In one embodiment of the invention the antibacterial agent comprises an antibiotic in the form of a substantially insoluble salt in an aqueous suspension. Preferably, the antibiotic agent is a substantially insoluble salt of a synthetic penicillin such as cloxacillin.

Most preferably the antibiotic comprises cloxacillin benzathine.

Preferably the antibiotic is in a micronised form having an average dimension of less than 25μ. Preferably a substantial proportion of the antibiotic has an average dimension of less than 10μ.

Preferably the composition is a unit dose. Typically the composition contains 600 mg of cloxacillin as cloxacillin benzathine.

In one embodiment of the invention antibacterial agent is present in the gel base.

Alternatively the antibacterial formulation and the seal formulation are separate.

In another embodiment of the invention the gel comprises a polyethylene gel. The gel may be based on low density polyethylene or on high density polyethylene.

The invention also provides a veterinary composition for use in the prophylaxis as treatment of mammary disorders in non-human animals during an animals' dry period.

Detailed Description of the Invention

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE A

A veterinary composition comprising
a first antibiotic - containing injector (1A) and a second seal-containing injector (2A) were prepared as follows:

INJECTOR 1A

Component	g/Kg	Function
Cloxacillin Benzathine	212.6	Antibiotic
PVP	0.59	Suspension Aid
Sodium Citrate	7.87	Buffer
Tween 80	0.983	Surfactant
EDTA (disodium)	0.0787	Cation Scavenger
Antifoam M30	0.0157	Production Aid
Water for Injection	QS	Aqueous Vehicle

* (i) will be adjusted depending on potency

(ii) the cloxacillin benzathine was in a micronised form having an average dimension less than 25μ with approximately 75% less than 15μ and 50% less than 10μ and 85% was greater than 2μ.

(1) Place most of the water for injection in a production vessel.

(2) Add and dissolve separately, sodium citrate, E.D.T.A., P.V.P. and Tween 80. Mix well.

(3) Add antifoam and mix well, the solution will have a slight haze.

(4) Add and suspend Cloxacillin Benzathine and homogenise for 15 minutes.

(5) Bring to final weight with addition of further water for injection.

(6) Fill 3.6g into intramammary injectors.

This formulation is stable when subjected to extended storage periods in its proposed marketing container.

We have surprisingly found that cloxacillin benzathine in an aqueous base gives rapid absorption in a very short time period.

A number of studies have been conducted in dry cows to establish the following : -

Study 1: Bioavailability of cloxacillin in bovine colostrum following intramammary infusion of Injector 1A.

Study 2: Residues of cloxacillin in bovine colostrum following intramammary infusion of the Injector 1A.

Study 3: Irritancy of aqueous cloxacillin in the bovine mammary gland.

The results can be summarised as follows.

<u>INJECTOR 1A - Study 1</u>

A total of 8 cows were infused with Injector 1A and drug levels were measured in colostrum for a period of 144 hours following infusion. A peak of 5233.4 µg/ml was seen one hour post infusion. This declined exponentially and no drug was detectable at 6 days post infusion. The results are presented graphically in Fig. 1. These results are precisely in line with the concept of a teat seal as described herein with a high initial peak effectively sterilizing the udder, with the second Injector providing a barrier to ingress of pathogens thereafter. This provides the advantages of reduced risk

of drug residues both to the producer and consumer based upon a unique dry cow antibiotic profile.

Fig. 1 is a graphic representation of the results of this study.

Fig. 2 is a log transformation of the results of Fig. 1.

These graphs illustrate a linear decline in drug levels over time which is an ideal pharmacokinetic profile.

INJECTOR 1A - Study 2

Study 2 was conducted to specifically determine the end point for milk withholding. Animals were infused in each of four quarters with the first Injector. Samples were taken every 24 hours and analysed for cloxacillin levels. Eight days after administration of Injector 1A the levels of drug were below the acceptable maximum residue level for cloxacillin.

INJECTOR 1A - Study 3

This study involved an assessment of the irritancy of the aqueous cloxacillin formulation in the bovine udder. It was found that cloxacillin is mildly irritant in the bovine udder but has no effect on milk yield and the somatic cell count returns to normal 72 hours after infusion.

From these studies it can be concluded that cloxacillin in an aqueous suspension offers a safe and effective means of controlling mastitis in the dry cow and offers significant advantages over existing preparations especially with regard to consumer health and animal welfare.

INJECTOR TYPE 2A

Various gels based on liquid paraffin with aluminium stearate were prepared.

Formulation	Mass Constituents	YV/(Nm^{-2})
2A1	3.5g 14% AS-LP gel + 37%BSN + 0.1%Ac	110.3
2A2	7.0g 14% AS-LP gel + 37%BSN + 0.1%Ac	110.3
2A3	3.5g 14% AS-LP gel + 37%BSN + 0.1%Ac	215.5

LP = Liquid Paraffin
BSN = Bismuth Subnitrate
Ac = Acriflavin
AS = Aluminium Monostearate
YV = Yield value - (A measure of the relative fluidity of the gel. Low yield values indicate a more liquid gel).

Products 2A1 to 2A3 were considered appropriate candidates for use as test seals.

An ideal teat seal should have the following characteristics :

1. It should be non-irritant to the bovine udder;

2. Persistence - the seal should remain in situ for the duration of the dry cow period;

3. Consistency - the seal should not break up within the udder;

4. Compatibility - the seal should be compatible with the antibiotic formulation used in association with it, either aqueous or oily;

5. Ease of Removal - at the end of the dry period, the seal should be readily removable for the udder and not give rise to persistent residues of either the seal or antibiotic.

Irritancy of the seals was the first characteristic to be assessed as any product which was irritant would have to be rejected irrespective of its performance against the other criteria. Irritancy was measured by conducting somatic cell counts in treated and untreated quarters of lactating cows and comparing these results by measuring area under the curve ratios using the following formula:

$$\text{AUC Ratio} = \frac{\text{AUC of treated quarter}}{\text{AUC of untreated quarter}}$$

This allows for a relative assessment of the various seal formulae.

Formulation	AUC Ratio	Peak (cells/ml)	Condition of milk	Duration before return to pre-dose level (hours)
2A1	1.25	9.0×10^5	Normal	160
2A2	1.33	1.0×10^9	Normal	144
2A3	1.28	8.5×10^5	Normal	160

Formulations 2A1 and 2A3 were considered appropriate for further investigation. It was concluded that AS-LP gels are viable candidates for sealing teats.

In vitro studies have shown that whilst AS-LP gels have relatively high yield values, their tensile strength is not as great as other possible seal formulations. The relative merits of these two properties were studied by X-ray analysis of various formulations in dry cows.

A series of studies were undertaken to optimise these parameters :

INJECTOR TYPE 2A - Study 1

Formulation	Gel former %	LP %	AC %	BSN %	Mass(g)	P g cm^3	YV Nm^{-2}
2A1	8.8 AS	54.1	0.1	37	7.0	1.32	110.0

AS = Aluminium Stearate
LP = Liquid Paraffin
AC = Acriflavin
BSN = Bismuth Subnitrate
p = Density
YV = Yield Value

The test formulation was infused into quarters of dry cows. The effectiveness of sealing was measured by X-ray analysis. In addition the mass of seal recovered, % BSN recovered and the effective seal duration [ESD] were estimated.

Formulation	ESD (days)	Mass of seal recovered (%)	BSN recovered
2A	28.5 ± 13.1	8.19 (117.1)	64.1

The mass of seal recovered was in excess of that applied probably due to the presence of aqueous material.

INJECTOR TYPE 2A - Study 2

The effect of the product volume and density was examined in another series of X-ray studies.

Formulation	Gel former %	LP %	AC %	BSN %	Mass g	P g cm^3	YV Nm^{-2}
2A4	3.1 AS	31.8	0.1	65	5.0	1.70	161.7
2A5	3.1 AS	31.8	0.1	65	10.0	1.70	161.7

The results of these studies are shown in the table below:

Formulation	Mass(g)* recovered (%)	% BSN ** recovered
2A4	2.47 (49.4)	89.8
2A5	4.52 (45.2)	100.2

* Adjusted for water content

** % BSN were higher than in the previous study indicating a greater integrity of seal. As this trial was of a shorter duration than study 1, this may have been a contributing factor. However, increasing the density and reducing the volume had a clearly beneficial effect on the product performance.

INJECTOR TYPE 2A - Study 3

As it is intended to use the teat seal in conjunction with an antibiotic preparation this study looked at the effect of an aqueous and oily based antibiotic suspension on seal integrity over time. Additionally, the mass of seal was reduced to 3.5g to see if this could further enhance the seals effectiveness.

Products used are given in the table below :

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}	Anti-biotic
2A6	3.1% AS	31.8	0.1	65	3.5	1.70	161.7	Oily
A6'	3.1% AS	31.8	0.1	65	3.5	1.70	161.7	Aq.

The products were then examined for their effective seal duration [ESD].

Formulation	ESD (days)	Recovery of material (g)	BSN Recovery %	BSN recovery in fluid portion ppm
2A6	47.8 ± 13.5	0	0	2191
2A6[1]	63.3 ± 5.4	2.06	75.2	117

A combination of a seal and an aqueous based antibiotic offers a superior combination to a seal and an oily based antibiotic. This can be deduced from the fact that the ESD's for the seal/aqueous combinations were significantly better than those for oily combination. This is further evidenced by the high BSN recoveries (>75%) for the aqueous products, indicating retention of seal in situ. In contrast, the amount of bismuth found in the fluid portion at parturition was far lower for the aqueous than the oily combination. This shows that there was a larger degree of dispersal of the seal into the udder with the oily combinations.

The amount of BSN lost in absolute terms can be calculated as follows :

A x B x M = Loss of BSN (g)
A = % BSN lost.
B = % of BSN in product
M = Mass of Product

Using the formula, product 2A1 lost 1.30 g. 2A6[1] lost 0.57g. Considering that product 2A6[1] was in situ for 70 days as compared to 49 days for 2A1, this demonstrates at least a 2-3 fold reduction in BSN loss and a major improvement in product design.

PREFERRED METHOD OF MANUFACTURE FOR INJECTOR TYPE 2A

	Gm/Kg
Aluminium Stearate (Alugel 30 D.F.)	48.9
Heavy Liquid Paraffin	300.4
Bismuth Subnitrate	650.00
Acriflavin (Pigment)	0.994

Each injector contains 3.5g.

The aluminium stearate used is a distearate compound having a melting point in the region of 150°C to 160°C.

Bismuth subnitrate ($6Bi_2O_3.5N_2O_5.9H_2O$) is a white, slightly hydroscopic powder.

(1) Place heavy liquid paraffin in reactor vessel. heat to 160°C for one hour. Cool to 40°C.

(2) Start emulsifiers and mixers and add the aluminium stearate. Heat to 145°C ± 5°C and maintain for one hour. Cool to 40°C.

(3) Add and blend the Bismuth Subnitrate and Acriflavin.

(4) Fill 3.5 g into intramammary injector.

EXAMPLE B

A veterinary composition was prepared comprising a first antibiotic-containing injector having the same formulation as Injector 1A described above and a second seal injector 2B as described below.

INJECTOR TYPE 2B

Various gel based on liquid paraffin with polyethylene were prepared. Two grades of polyethylene were used in manufacturing the gels: low density (LDPE) and high density (HDPE). They differed in the degree of side chain branching but produced similar gels.

Formulation	Mass	Constituents	YV (NM^{-2})
2B1	3.5g	3% HDPE - LP gel + 37% BSN + 0.1%Ac	40.9
2B2	7.0g	3% HDPE - LP gel + 35% BSN + 0.1%Ac	40.9
2B3	7.0g	5% HDPE - LP gel + 37% BSN + 0.1%Ac	110.0
2B4	7.0g	5% HDPE - LP gel + 37% BSN + 0.1%Ac	220.3
2B5	3.5g	3% HDPE - LP gel + 37% BSN + 0.1%Ac	65.8
2B6	7.0g	3% HDPE - LP gel + 37% BSN* + 0.1%Ac	36.6
2B7	7.0g	3% LDPE - LP gel + 37% BSN* + 0.1%Ac	54.1

LP = Liquid Paraffin

BSN= Bismuth Subnitrate

Ac = Acriflavin

YV = Yield value - (A measure of the relative fluidity of the gel. Low yield values indicate a more liquid gel).

* = BSN was in micronised form.

Products 2B1 and 2B7 were considered appropriate candidates for use as test seals. An ideal teat seal should have the following characteristics:

1. It should be non-irritant to the bovine udder;

2. Persistence - the seal should remain in situ for the duration of the dry cow period;

3. Consistency - the seal should not break up within the udder;

4. Compatibility - the seal should be compatible with the antibiotic formulation used in association with it, either aqueous or oily;

5. Ease of Removal - at the end of the dry period, the seal should be easily removable for the udder and not give rise to persistent residues of either the seal or antibiotic.

Irritancy of the seals was the first characteristic to be assessed as any product which was irritant would have to be rejected irrespective of its performance against the other criteria. Irritancy was measured by conducting somatic cell counts in treated and untreated quarters of lactating cows and comparing these results by measuring area under the curve ratios using the following formula:

$$\text{AUC Ratio} = \frac{\text{AUC of treated quarter}}{\text{AUC of untreated quarter}}$$

This allows for a relative assessment of the various seal formulae.

Formulation	AUC RATIO	PEAK (CELLS/mL)	CONDITION OF MILK	DURATION BEFORE RETURN TO PRE-DOSE LEVEL (HOURS)
2B1	17.0	5.3×10^6	N	160
2B2	4.8	2.4×10^6	N	160
2B3	16.4	$>3 \times 10^6$	N	184
2B4	3.7	1.7×10^6	N	136
2B5	10.8	1.0×10^6	N	112
2B6	13.0	7.0×10^6	N	120
2B7	51.8	$>1.0 \times 10^7$	C	112

N = Normal
C = Clotted

Formulations 2B1 and 2B5 were considered appropriate for further investigation. 2B6 and 2B7 (micronised Bismuth Subnitrate) were excluded on the basis of there being more irritant that the other formulas tested and having no significant advantages. Thus, it is concluded that PE-LP gels are viable candidates for sealing teats.

In vitro studies have shown that PE-LP gels have high tensile strengths for relatively low yield values. The merits of these two properties were studied by X-ray analysis of various PE-LP formulations in dry cows.

A series of studies were undertaken to optimise these parameters:

INJECTOR TYPE 2B - Study 1

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}
2B3	3.1% PE	59.8	0.1	37	7.0	1.32	136.6
2B2	1.9% PE	61.0	0.1	37	7.0	1.32	40.0
2B3[1]	3.1% PE	59.8	0.1	37	7.0	1.32	220.3

PE = Polyethylene
LP = Liquid Paraffin
AC = Acriflavin
BSN= Bismuth Subnitrate
P = Density
YV = Yield Value
2B3[1]= Formulation is identical to 2B3. Gel was formed using different temperature profile, leading to different yield values.

Each of the test formulations was infused into quarters of dry cows. The effectiveness of sealing was measured by X-ray analysis. In addition to mass of seal recovered, %

BSN recovered and the effective seal duration [ESD] were estimated.

Formulation	ESD (days)	Mass of Seal recovered (%)	BSN recovered
2B3	47.3 ± 16.0	0.62 (8.81)	40.8
2B2	54.1 ± 10.4	3.00 (43.0)	40.0
2B3[1]	49.0 ± 12.9	1.38 (19.7)	44.6

There was a direct correlation between the ESD and the mass of seal recovered for these products.

INJECTOR TYPE 2B - Study 2

The effect of the product volume and density was examined in another series of X-ray studies.

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}
2B8	1.7% PE	33.2	0.1	65	5.0	1.70	216.3
2B9	1.7% PE	33.2	0.1	65	10.0	1.70	216.3

The results of these studies are shown in table below:

Formulation	Mass (g) * recovered (%)	% BSN ** recovered
2B8	3.78 (75.6)	85.6
2B9	3.92 (39.2)	92.2

* Adjusted for water content

** % BSN were greater than in the previous study indicating a greater integrity of seal. As this trial was of a shorter duration than study 1, this may have

been a contributing factor. However, increasing the density and reducing the volume had a clearly beneficial effect on the product performance.

INJECTOR TYPE 2B - Study 3

As it is intended to use the teat seal in conjunction with an antibiotic preparation this study looked at the effect of an aqueous and oily based antibiotic suspension on seal integrity over time. Additionally, the mass of seal was reduced to 3.5g to see if this could further enhance the seals effectiveness.

Products used are given in the table below:

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}	Anti-biotic
2B8	1.7% PE	33.2	0.1	65	3.5	1.70	216.3	Oily
2B9	1.7% PE	33.2	0.1	65	3.5	1.70	216.3	Aq.

The products were then examined for their effective seal duration [ESD].

Formulation	ESD (days)	Recovery of material (g)	BSN Recovery %	BSN Recovery in fluid proportion ppm
B8	56.8 ± 13.9	0	0 .	1200
B9	60.3 ± 8.2	0.793	77.6	147

A combination of seal and a non aqueous based antibiotic offers a superior combination to seal and an oily based antibiotic. This can be deduced from the fact that the ESD's for the seal/aqueous combinations were significantly

better than those for oily combinations. This is further evidenced by the high BSN recoveries (>75%) for the aqueous products, indicating retention of seal in situ. In contrast the amount of bismuth found in the fluid portion at parturition was far lower for the aqueous than the oily combination. This shows that there was a larger degree of dispersal of the seal into the udder with the oily combinations.

In conclusion, the use of polyethylene as a gelling agent in combination with heavy metal salts in a teat seal product in combination with an aqueous based antibiotic system provides a product with the desired properties as earlier outlined which should be efficacious in the treatment and prophylaxis of dry cow mastitis.

PREFERRED METHOD OF MANUFACTURE FOR INJECTOR TYPE 2B

	Gm/Kg
H.D.P.E.	17.00
Heavy Liquid Paraffin	332.00
Bismuth Subnitrate	650.00
Acriflavin (Pigment)	0.994

Each injector contains 3.5g.

Bismuth subnitrate ($6Bi_2O_3.5N_2O_5.9H_2O$) is a white, slightly hydroscopic powder

(1) Place heavy liquid paraffin in reactor vessel. Heat to 160°C for one hour. Cool to 40°C.

(2) Start emulsifiers and mixers and add the H.D.P.E. Heat to 145°C ± 5°C and maintain for one hour. Cool to 40°C.

(3) Add and blend the Bismuth Subnitrate and Acriflavin.

(4) Fill 3.5g into intramammary injector.

In vivo studies have suprisingly shown that levels of greater than 40% Bismuth Subnitrate produces a seal product that remains in situ and shows less break-up than seals with lower levels of Bismuth Subnitrate. In addition, because the product is more dense a lesser quantity is required to achieve an effective seal.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A veterinary composition for intramammary use in non-human animals comprising an antibacterial formulation, and a seal formulation, the seal formulation comprising a gel base and a non-toxic heavy metal salt in the base, wherein the heavy metal salt is present in an amount of at least 40% by weight of the base.

2. A veterinary composition as claimed in claim 1 wherein the heavy metal salt is present in an amount of between 50% and 75% by weight.

3. A veterinary composition as claimed in claim 1 or 2 wherein the heavy metal salt is present in an amount of approximately 65% by weight of the base.

4. A veterinary composition as claimed in any of claims 1 to 3 wherein the salt is bismuth sub-nitrate.

5. A veterinary composition as claimed in any preceding claim wherein the base is a gel based on the aluminium stearate.

6. A veterinary composition as claimed in any preceding claim wherein the gel includes a vehicle such as liquid paraffin.

7. A veterinary composition as claimed in any of claims to 1 to 6 wherein the antibacterial agent comprises an antibiotic in the form of a substantially insoluble salt in an aqueous suspension.

8. A veterinary composition as claimed in claim 7 wherein the antibiotic comprises a substantially insoluble salt of a synthetic penicillin.

9. A veterinary composition as claimed in claim 8 wherein the synthetic penicillin is cloxacillin.

10. A veterinary composition as claimed in claim 10 wherein the antibiotic comprises cloxacillin benzathine.

11. A veterinary composition as claimed in any of claims 7 to 10 wherein the antibiotic is in a micronised form having an average dimension of less than 25μ.

12. A veterinary composition as claimed in claim 11 wherein a substantial proportion of the antibiotic has an average dimension of less than 10μ.

13. A veterinary composition as claimed in any of claims 7 to 12 wherein the antibiotic is a unit dose.

14. A veterinary composition as claimed in claim 13 wherein the composition contains 600 mg of cloxacillin as cloxacillin benzathine.

15. A veterinary composition as claimed in any preceding claim wherein the antibacterial agent is present in the gel base.

16. A veterinary composition as claimed in claim 1 to 14 wherein the antibacterial formulation and the seal formulation are separate.

17. A veterinary composition as claimed in any preceding claim for use in the prophylaxis as treatment of mammary disorders in non-human animals during an animals' dry period.

18. A veterinary composition substantially as hereinbefore described with reference to the drawings and examples.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report)	Application number GB 9325161.9
Relevant Technical Fields (i) UK Cl (Ed.M) A5B (BKB, BLD) (ii) Int Cl (Ed.5) A61K	Search Examiner M R WENDT Date of completion of Search 14 MARCH 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES: WPI, CLAIMS, CAS ONLINE, JAPIO, BIOSIS, EMBASE, MEDLINE	Documents considered relevant following a search in respect of Claims :- 1-18

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
Y	GB 1456349	(UPJOHN) See Claims 1 and 7, page 2 lines 15-32	1, 4, 5, 8
Y	GB 1441747	(LAZONBY) See whole document	1, 4, 5, 8
Y	EP 0271306 A2	(BEECHAM) See claims, page 2 lines 51-53	1, 4, 5, 8
Y	US 4172138	(RHODES) See claims, column 1 lines 54-63	1, 4, 5, 8
A	Irish Journal of Agricultural Research 16: 1977, pages 293-299 See page 29, Experiment 2		1

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).